REMARKS

Claims 25, 28, and 31 have been amended to delete non-elected subject matter and claims 33-34, 36-37, and 39-40 directed to this subject matter have been canceled. This amendment is made after final; however, as this involves only cancellation of claims and of non-elected subject matter, it is believed that entry of the amendment is proper.

The sole outstanding rejection is made under 35 U.S.C. §§ 101/112, first paragraph, asserting that the method has no practical utility, and thus the application fails to teach how to use the invention.

This rejection appears to be based on the following concepts:

1. It is asserted that compounds identified as agonists or antagonists of T-type calcium channels may not in fact be useful in treating any disease. No compounds are said to have been isolated by the claimed method that treat a specific disease. (This appears to be the gist of the arguments set forth on pages 6-8 of the Office action; see also pages 11 and 14-16 of the Office action.) It is stated that additional experimentation would be required to determine which disease state, if any, is a result of T-type calcium ion channel dysfunction; presumably this is based on the assertion that all of the diseases listed cannot be associated with such dysfunction. (See page 10 of the Office action.)

2. The fact that other U.S. patents, specifically 6,358,706 and 6,309,858 have issued to other T-type channels is asserted not to create a precedent which requires an issuance of a patent in the present application. (This is the argument set forth on pages 8-9 of the Office action.)

3. It is known that there are materials that inhibit calcium ion channel activity, such as magnesium ion or nickel ion or ethanol, that are presumably impractical as pharmaceuticals to treat

diseases. Therefore, it is asserted that this shows that compounds identified by the invention method will not be successful pharmaceuticals. (See pages 9-10 of the Office action.)

4. An article by Sylvie, *et al., TIPS* (1997) 18:37-42 is cited which is said to show that there is much still to be learned about the function and role of T-type channels. An article by Williams is cited to show calcium channels in neurons have diverse functions. (See pages 11-13 of the Office action.)

5. It is hinted in several places that claims which include α_1 subunits functional as T-type ion channels encoded by nucleotide sequences which hybridize under specific stringency conditions to SEQ ID NO: 23 are particularly suspect. (See page 14, middle of the page.)

6. An article by Bork, *Nature Genetics* (1998) 18:313-318 is cited to show that identification of function by homology to proteins of known function may be erroneous; a further article by Karp, *Bioinformatics* (1998) 14:753-754 is cited as well. (See pages 16-18.)

The Examiner's summary of these arguments appears on pages 18-19.

Applicants will respond to each of these in turn.

1. With respect to diseases that could be treated by compounds identified by the method of the invention, it has already been called to the attention of the Office that page 9 of the specification, lines 5-7, lists a number of diseases that are associated with T-type channel defects. The specification further states on page 9 that it is directed to a method for evaluating compounds as pharmacological modifiers of the function of calcium ion channels of the invention (see page 9, lines 1-3). Thus, the specification clearly identifies diseases that are sufficiently related to T-type calcium ion channel defects that compounds identified by the methods of the invention can be used to treat them. The Office may be correct that further experimentation is necessary to verify that the

compounds so identified will in fact be successful in treating these diseases. However, this is not a barrier to patentability. In the previous response, applicants cited the Guidelines issued by the Office in evaluating such claims. As stated in these Guidelines themselves,

> Courts have found repeatedly that the mere identification of a pharmacological activity of a compound that is relevant to an asserted pharmacological use provides an "immediate benefit to the public" and thus satisfies the utility requirement. As the CCPA held in Nelson v. Bowler:
>
> > Knowledge of the pharmacological activity of any compound is obviously beneficial to the public. It is inherently faster and easier to combat illnesses and alleviate symptoms when the medical profession is armed with an arsenal of chemicals having known pharmacological activities. Since it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible, we conclude that adequate proof of any such activity constitutes a showing of practical utility.
>
> Similarly, courts have found utility for therapeutic inventions despite the fact that an applicant is at a very early stage in the development of a pharmaceutical product or therapeutic regimen based on a claimed pharmacological or bioactive compound or composition. Accordingly, Office personnel should not construe § 101, under the logic of "practical" utility or otherwise, to require that an applicant demonstrate that a therapeutic agent based on a claimed invention is a safe or fully effective drug for humans.

This is exactly the situation here. The method of the invention identifies agonists and antagonists of T-type calcium ion channels. There is indeed more work to be done before any of these compounds becomes a drug. The Guidelines are quite clear that this is expected. No response to this argument, made previously, is found in the outstanding Office action.

Further, if a number of modulators of calcium ion channels have been found to fall short of success in actually treating the target conditions, this is itself further proof of the utility of the

present invention. If present candidates are not useful, it clearly behooves practitioners to identify additional candidates that may lead to success.

But it has been shown that T-channel blockers are successful. How can the Office ignore the documents that were submitted with the response filed 26 March 2004, which showed actual clinical studies demonstrating that the T-type calcium channel blocker mibefradil is effective in reducing blood pressures and heart rate and prevents stroke and mortality in patents with high blood pressure?

2. With respect to the second assertion made by the Office, applicants are well aware that there is no binding precedent provided by issuance of patents on similar technology. However, applicants believe that they have a right to expect that the criteria applied to the examination of all patent applications will be consistent. It is apparent that the Office has correctly applied the Guidelines cited above in issuing the two patents previously cited. If data are the issue, it is noted that there are no data in either of these patents that demonstrate that compounds that could be identified by their activity with respect to the isoforms of the T-type channels described in these patents.

For example, U.S. 6,309,858 merely states in a single paragraph that candidate compounds are useful in the treatment or prophylaxis of pain including, but not limited to, peripheral pain, peripheral neuropathies, pain caused by trauma or toxic compounds; diabetic neuropathy, cancer pain, and the like (column 19, lines 63-67). There is nothing further that discloses any nexus between the T-type channels described there and any diseases. The disclosure is directly comparable to that in the present case.

Similarly, in U.S. 6,358,706, column 17, line 17-column 18, line 5 lists a plethora of conditions that are asserted to be treatable or potentially treatable by the modulators of the T-type channels disclosed there. If the objection of the Office is that the present application lists too many alternatives, applicants point out that they are vastly outdone by the list in the '706 patent. Further, the indications set forth in the present specification also occur in this list.

Thus, the very same criticisms that are leveled against the possible utility of the compounds identified by the present methods could have been leveled with respect to the analogous methods which would constitute the use of the T-type calcium ion channels described in these patents. As required by the Guidelines, in the examination of these patents, the Office apparently recognized that, as stated in *Nelson v. Bowler & Crossley*, 626 F2d 853, 206 USPQ 881 (CCPA 1980), "it is crucial to provide researchers with an incentive to disclose pharmacological activities in as many compounds as possible" because "it is inherently faster and easier to combat illnesses and alleviate symptoms when medical profession is armed with an arsenal of chemicals having known pharmacological activities."

The ability to modulate calcium ion channel activities is clearly a pharmacological activity, and applicants have complied with the requirements for patentability according to the Guidelines.

3. With respect to the third criticism, applicants believe that it is insulting to the accomplishments of those of ordinary skill in the art to assert that practitioners would not be able to distinguish between suitable candidate pharmaceuticals and those that are not suitable among substances that inhibit or otherwise modulate calcium channel activity. To assert that because some modulators such as nickel ion, magnesium ion, and ethanol are not useful pharmaceuticals, there is

no useful correspondence between modulating activity and pharmaceutical utility, is to ignore the informal discretion of the skilled practitioner.

4. With respect to the fourth item, relating to the Sylvie article, suffice it to say that this article merely outlines the expected further experimentation that would be required once candidate compounds are identified, which experimentation is considered acceptable according to the Guidelines.

5. With respect to the fifth issue, relating to α_1 subunits encoded by nucleotide sequences that hybridize to SEQ ID NO: 23, applicants merely point out that it is required that the hybridizing sequence encode a functional T-type calcium ion channel α_1 subunit and thus substantially full-length nucleotide sequences would be required. Applicants further point out that sequences which fail to encode functional subunits are not included in the claims. In addition, this concern does not apply to claims 32, 35, and 38.

6. With respect to the sixth item, regarding identification of sequences by homology, applicants point out that the functionality of the calcium ion channel encoded by SEQ ID NO: 23 has been verified experimentally as set forth in the specification in Example 25 on page 25, beginning at line 18. Therefore, the arguments with respect to homology appear irrelevant in this case.

In summary, and in direct response to the items enumerated on pages 18-19 of the Office action:

Paragraph 1: The α_1 subunit encoded by the nucleotide sequences that hybridize to SEQ ID NO: 23 must be of sufficient length to encode a functional α_1 T-type calcium ion channel subunit. The specification teaches how to use the specified α_1 subunit because the claimed method results in

identification of candidate compounds for treatment of specified diseases enumerated in the specification. This is all that is required by the decisions of the Federal Circuit and the Utility Guidelines set forth by the Office.

Paragraph 2: It is irrelevant whether publications before the priority application was filed do or do not demonstrate the α_1 subunit encoded by SEQ ID NO: 23 or sequences that hybridize to it have functional utility. It is not the function of the prior art to establish utility, it is the function of the specification itself. The specification does this by indicating that candidate compounds for treating specified diseases can be identified using the α_1 subunits specified herein.

Paragraph 3: No reason has been cited for the conclusion that the declaration by Dr. Snutch does not demonstrate that the claimed screening methods are useful for identifying molecules that treat specific T-type calcium channel related diseases. This statement is entirely without support.

Paragraph 4: It has already been explained that the Guidelines do not require that every compound identified or indeed that any compounds identified as agonists or antagonists of calcium ion channels as described would ultimately turn out to be successful pharmaceuticals. This statement is equally applicable to Paragraph 5.

Paragraph 6: Applicants' position has been explained – the public at large and applicants in particular have a right to expect that the Office will not act in an arbitrary manner, granting patents to some and denying patents to others based on substantially similar facts. It is not a question of precedent, but a question of consistency.

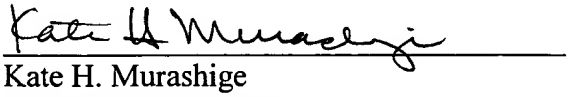
Conclusion

It is clear from decisions quoted in the Guidelines and from the Guidelines themselves that identification of candidate compounds for treatment of diseases is an acceptable utility to support

patentability of the compounds themselves, and therefore of the methods to identify them. Specific diseases for which these compounds are candidates have been identified in the specification. There is no showing on the part of the Office that such diseases are unreasonable targets or that the nexus of these diseases with T-type calcium ion channel activity is contrary to scientific principles or common sense. Therefore, applicants believe that the assertions of the specification must be taken at face value, especially in light of the declaration of Dr. Snutch, to which no adequate response has been received. Accordingly, applicants believe that the claims as amended, claims 25-32, 35, and 38 are in position for allowance and passage of these claims to issue is respectfully requested.

In the unlikely event that the transmittal letter is separated from this document and the Patent Office determines that an extension and/or other relief is required, applicants petition for any required relief including extensions of time and authorize the Assistant Commissioner to charge the cost of such petitions and/or other fees due in connection with the filing of this document to **Deposit Account No. 03-1952** referencing docket No. 381092000720.

Respectfully submitted,

Dated: April 25, 2005 By: 

Kate H. Murashige
Registration No. 29,959

Morrison & Foerster LLP
3811 Valley Centre Drive,
Suite 500
San Diego, California 92130-2332
Telephone: (858) 720-5112
Facsimile: (858) 720-5125